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Spate of Suspensions of Academic Research Spurs Questions About Federal Strategy: A U.S. agency, its own future uncertain, unsettles college officials with its crackdown

By JEFFREY BRAINARD

Washington DC

For much of the 1990's, scientists at academic health centers benefited from a surge of clinical research that brought their institutions money, prestige, and patients seeking cutting-edge cures. But since October 1998, those researchers have increasingly run scared.

In the past 16 months, federal regulators have imposed an unprecedented series of suspensions on campus research efforts involving human participants, after finding that some institutions were not following mandatory guidelines meant to safeguard the safety and dignity of the participants.

Medical centers affiliated with seven universities and one veterans' hospital have had to temporarily halt research. The latest suspensions came in January -- at the University of Alabama at Birmingham, the University of Pennsylvania, and Virginia Commonwealth University.

Across the country, university administrators and researchers are worried, even panicked, that the same thing could happen at their institutions, with millions of dollars of research funds from the National Institutes of Health and pharmaceutical companies at stake. At the same time, the suspensions raise questions about whether campuses are putting lives at risk, or whether the government is overreaching in enforcing its rules.

These concerns have prompted a debate that could eventually reshape relations between universities and the N.I.H.'s Office for Protection from Research Risks, which issued most of the suspensions.

Some university officials have called the actions unreasonable, and have said the office should refocus its role to balance enforcement with greater assistance to institutions. This idea appears to have found support among officials at the Department of Health and Human Services, which oversees the N.I.H., and has announced that it will take direct control of the research-risks office. But others, who believe universities have not done

enough to protect human research subjects, fear a dilution of the office's enforcement activity.

The Food and Drug Administration is also becoming part of the equation. Using its authority for protecting patients in trials of new drugs and therapies, the F.D.A. has joined the O.P.R.R. in suspending three of the eight institutions. In January, the F.D.A. suspended gene-therapy trials at the University of Pennsylvania following the death of a teenage patient.

The chief grievance against the O.P.R.R. is that its suspensions have focused largely on universities' failure to document their oversight of experiments involving humans, and to follow federally mandated procedures. Critics note that several of the O.P.R.R.'s suspensions included no allegations that human participants had been injured by risky experiments or had not given informed consent.

The office has said, for example, that the universities' institutional review boards, or I.R.B.'s, failed to assess continuing research projects at least annually, and neglected to review the full text of grant applications for research projects. I.R.B.'s are composed of university researchers and at least one community representative. The government relies on the panels to judge whether proposed experiments are unreasonably risky, and to make sure that participants are adequately advised of potential hazards.

Among the paperwork deficiencies, "any one of those things does not seem like that big a deal," said Robert J. Levine, professor of medicine at Yale University and chairman of its I.R.B. "If you don't like the way an I.R.B. is keeping minutes, you can say so, but you don't need to close an institution to bring about change of this sort." Dr. Levine is also the editor of a journal called RB: A Review of Human Subjects Research.

The director of the O.P.R.R., Gary B. Ellis, said that the agency generally halts research only after giving institutions time to correct deficiencies. More broadly, though, he insisted that the spate of suspensions does not represent a deliberate crackdown; the agency, said Mr. Ellis, has been struggling to work through a backlog of 120 open investigations, and suspensions can be the result. The O.P.R.R.'s suspensions affect all research financed by the Department of Health and Human Services.

"It doesn't feel like there's any advance in the pace of O.P.R.R.'s oversight from where I sit," said Dr. Ellis. "Our feeling is one of being overwhelmed." The office has a budget of $3-million, with three investigators assigned to handle complaints involving human subjects. They oversee an estimated 3,000 to 5,000 I.R.B.'s, many of which are associated with academic health centers.

Some university officials see the recent suspensions as driven primarily by several government reports in recent years that found I.R.B.'s to be doing too little to protect human research subjects.

But people serving on I.R.B.'s argue that most do an adequate job, despite being burdened with large caseloads and minimal staff support.

"We used to be less concerned with dotting the i's than we are now," said Helen McGough, manager of the human-subjects division at the University of Washington, who helps coordinate the three I.R.B.'s there. "In the worst possible case, we would spend a lot of time making sure that the minutes were typed properly. I can see that the more energy is devoted to procedural issues, the less time is devoted to substantive review."

Mr. Ellis disputes the contention that the suspensions primarily concerned administrative deficiencies. Several, he noted, responded to cases in which participants in research studies were harmed.

The O.P.R.R., for example, found fault with decisions by researchers at Rush-Presbyterian-St. Luke's Medical Center in Chicago to enroll three patients in a study of medication to treat strokes. Those three were ineligible because their symptoms from stroke made participation risky, the office found. One of the participants died a month after treatment.

And the O.P.R.R. faulted researchers at Virginia Commonwealth for mailing inappropriate questionnaires that asked twins sensitive questions about their family histories for a study on genetics.

"O.P.R.R.'s files are replete with offenses to human dignity, psychological injury, and physical injury," Mr. Ellis said. "If this were a focus on paperwork and bureaucratic nitpicking, it would be wrong and unproductive."

Inadequate documentation by I.R.B.'s suggests that they may be systematically failing to monitor the safety of research subjects in continuing studies, according to Mr. Ellis. That, he said, "could be more serious than a single incident involving a patient in the past." However, some federal requests for documentation seem to generate more work without clear improvements in protections for subjects, said Ms. McGough of the University of Washington.

Take, for example, the requirement that I.R.B. members read the complete text of all grant applications submitted by researchers using human subjects. In the past, I.R.B.'s at the University of Washington had received a short digest from researchers describing expected risks and benefits of the research, she said. Because the research-risks office faulted such practices in some of the recent suspensions, Washington's panel members now are asked to read the entire application, which typically runs 60 pages -- and can reach 200, Ms. McGough said.

"I'm not sure we're getting a whole lot of information from the time we're spending," she said.

The O.P.R.R. has insisted that the regulations require full review of the application, because I.R.B.'s appear to have ignored portions that did not describe the proposed research directly, but that could nevertheless be useful to the I.R.B. in judging the safety of trials. These included the qualifications of scientists conducting them, and descriptions of the settings in which the studies were to occur.

Mr. Ellis has also said that in several cases, researchers supplied different information to I.R.B.'s than they included in their grant applications -- an apparent violation of regulations.

"It's still a mystery to most of us what an I.R.B. is supposed to look at in a grant application," said a professor who heads the I.R.B. at a research university, and who spoke on condition of anonymity. "We don't want to leaf through a 100-page grant application looking for sections having to do with human subjects."

I.R.B. members may be exaggerating how much work that really takes, said David J. Rothman, professor of social medicine at Columbia University's College of Physicians and Surgeons, and a member of that university's I.R.B. Columbia's panel members routinely receive and review the full text of all grant applications, Mr. Rothman said. "Surely it is not beyond the ability of I.R.B. members to skim," he said.

University officials are also concerned about the rule that I.R.B.'s must review continuing-research studies at least yearly. Mr. Ellis has said the regulation is useful for considering new information about ethical and safety aspects of experiments.

Some I.R.B.'s have allowed individual members to screen studies, selecting only problematic ones for presentation to the full board for discussion. The O.P.R.R. allows such culling, but requires the board to approve or disapprove each study, including those that the reviewers decided raised no problems meriting the full board's discussion.

Instead of reviewing these one by one, the I.R.B. at the University of Alabama at Birmingham approved the continuing studies in blocks of 10, Mr. Ellis said. That was one of the deficiencies cited by the O.P.R.R. when it suspended research there.

But with Yale sponsoring 2,000 studies a year, the simple act of reviewing each annually -- even perfunctorily -- can burden I.R.B.'s excessively, Dr. Levine said.

Since the suspensions began, Yale's I.R.B. now receives two large carts loaded with files at each meeting, so that the full committee can participate in the annual reviews, he said. I.R.B. members spent an average of eight hours every two weeks preparing for or attending panel meetings, before the O.P.R.R.'s actions led to additional workload, he said. Now that figure has risen to about 11 or 12 hours every two weeks, Dr. Levine said.

I.R.B. members are generally unpaid and conduct research projects of their own, in addition to teaching and other duties.

"What you don't want to do is to take up their valuable time doing secretarial work," said the university's I.R.B. chairman who asked not to be named. "It's hard to recruit senior faculty to serve on the I.R.B. That's what you want -- really experienced, thoughtful people. It's always a struggle, and

now it's harder."

Complaints about I.R.B. workloads are neither unfamiliar nor unwelcome at the federal research-risks office. "My impression is that there is tremendous dedication by I.R.B.'s and their staffs all across the country," Mr. Ellis said. "Far too often, we see institutions leaving their I.R.B.'s at sea without proper support."

The solution, he said, is for institutions to expand the size, budgets, and staffs of their I.R.B.'s. But many university officials cite limited resources -- in part because of the cap on federal reimbursement of research-related overhead costs.

The O.P.R.R.'s spate of suspensions seems to have supplied the necessary leverage to pressure some university administrators to dig deeper, said Robert M. Nelson, associate professor of pediatrics and bioethics at the Medical College of Wisconsin. "If someone hasn't died" in an experiment, "or called the dean about a research project, then they assume the I.R.B. process is going fine -- and that's not necessarily the case," said Dr. Nelson.

However, the "hammer method" of the O.P.R.R., as Dr. Nelson calls it, may not be the most appropriate way to encourage universities to improve their oversight of human subjects. He and others hold high hopes for a forthcoming, voluntary system for accrediting I.R.B.'s and researchers who work with human subjects. An advocacy group called Public Responsibility in Medicine and Research (PRIM&R), which educates I.R.B.'s about government rules, is developing such a system, and is expected to issue a proposal later this year.

An accrediting body would visit an institution every five years and work with university officials to correct any deficiencies. This process could help foster a "culture of improvement" regarding human subjects, Dr. Nelson said, and a more proactive stance toward protecting them.

Still unclear is how the research-risks office's oversight role would change under this new model. But even without a shift to an accreditation system, the office's staff should work more closely with researchers and I.R.B.'s, said Dr. Levine of Yale.

"You have to have personnel who can appreciate the impact of their decisions," he said. "If you tell an organization that they're closing down all of their clinical research, that has many ramifications. And it can be a deadly blow to the career of a postdoctoral fellow. It has the potential to cut off people from protocols to get the best treatment they could get. There has got to be a willingness to search for less-draconian measures to encourage compliance."

Critics and supporters of O.P.R.R. believe that the Department of Health and Human Services has already signaled a desire to change the office's mission. It may include hiring a new director with a strong clinical background to replace Mr. Ellis, who some believe interprets rules too rigidly to work cooperatively with colleges.

By March, the office is expected to move from the N.I.H. to the office of Health and Human Services Secretary Donna Shalala. Ms. Shalala announced the shift in November, after it was recommended by a committee advising Harold E. Varmus, the former N.I.H. director. The panel said that having O.P.R.R. within N.I.H. presented the appearance of a conflict of interest, because the N.I.H. finances the research that the office regulates. The O.P.R.R. is to be renamed the Office for Human Research Protections.

Secretary Shalala also accepted a recommendation to make the O.P.R.R. director's job an appointed position, rather than a civil-service job. That means that a formal search for the opening must be held.

Some observers suggest that the new job description has been purposefully written in such a way to make it difficult for Mr. Ellis to become the top candidate. In particular, the job would require "national recognition for his/her accomplishments in scientific research, sufficient to be viewed by the research community as a statesman and authority in the areas under his/her purview."

Mr. Ellis did postdoctoral research in male reproductive biology at the beginning of his career, but it is unclear whether he would meet that new criteria. He said he had applied for the new position, but declined to comment further about it.

Even when the O.P.R.R. moves to the secretary's office, "there will be plenty of weight on the side of pushing forward with the research. You just want someone in the office that will put appropriate weight" on the concerns of human subjects, said Alexander M. Capron, a professor of law and medicine at the University of Southern California and a member of President Clinton's National Bioethics Advisory Commission. "If that agency pulls its punches because that office is principally concerned with the research function, then I think things get out of balance."

Department officials who are overseeing the move and job search, which closes this month, could not be reached for comment.

Indeed, some argue that moving the office to the Department of Health and Human Services would only reduce, but not eliminate, conflict-of-interest issues, because the N.I.H. is part of the department. Rep. Dennis J. Kucinich, a Democrat from Ohio, has introduced a bill to make the office an independent agency, with the director reporting to the president.

In the January 28 issue of the journal Science, two administrators at Duke University Medical Center -- the largest facility to receive one of the O.P.R.R. suspensions -- said that giving a single federal agency responsibility for overseeing research on human subjects could streamline redundancies that exist in enforcement by the O.P.R.R., F.D.A., and other agencies.

"Given the expansion of clinical research, it is time for a comprehensive review of subject-protection legislation and oversight that was developed in a

far different era," wrote Ralph Snyderman, chancellor of health affairs, and Edward W. Holmes, dean of the school of medicine. Duke's clinical trials have grown from 400 to 2,000 since the N.I.H.'s guidelines were first written, they noted.

They called for "an effective, simplified system that is understandable, that works, and that is adaptable to change."
